Contribution of alcohol use disorders to the burden of dementia in France 2008–13: a nationwide retrospective cohort study

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Summary

Background Dementia is a prevalent condition, affecting 5–7% of people aged 60 years and older, and a leading cause of disability in people aged 60 years and older globally. We aimed to examine the association between alcohol use disorders and dementia risk, with an emphasis on early-onset dementia (<65 years).

Methods We analysed a nationwide retrospective cohort of all adult (≥20 years) patients admitted to hospital in metropolitan France between 2008 and 2013. The primary exposure was alcohol use disorders and the main outcome was dementia, both defined by International Classification of Diseases, tenth revision discharge diagnosis codes. Characteristics of early-onset dementia were studied among prevalent cases in 2008–13. Associations of alcohol use disorders and other risk factors with dementia onset were analysed in multivariate Cox models among patients admitted to hospital in 2011–13 with no record of dementia in 2008–10.

Findings Of 31 624 156 adults discharged from French hospitals between 2008 and 2013, 1109 343 were diagnosed with dementia and were included in the analyses. Of the 57 353 (5·2%) cases of early-onset dementia, most were either alcohol-related by definition (22 338 [38·9%]) or had an additional diagnosis of alcohol use disorders (10 115 [17·6%]). Alcohol use disorders were the strongest modifiable risk factor for dementia onset, with an adjusted hazard ratio of 3.34 (95% CI 3·28–3·41) for women and 3·36 (3·31–3·41) for men. Alcohol use disorders remained associated with dementia onset for both sexes (adjusted hazard ratios >1·7) in sensitivity analyses on dementia case definition (including Alzheimer’s disease) or older study populations. Also, alcohol use disorders were significantly associated with all other risk factors for dementia onset (all p<0·0001).

Interpretation Alcohol use disorders were a major risk factor for onset of all types of dementia, and especially early-onset dementia. Thus, screening for heavy drinking should be part of regular medical care, with intervention or treatment being offered when necessary. Additionally, other alcohol policies should be considered to reduce heavy drinking in the general population.

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Background

Dementia is a clinical syndrome caused by brain damage and characterised by progressive deterioration in cognitive ability and capacity for independent living and functioning.1 It is a common condition, affecting 5–7% of people aged 60 years and older worldwide,2 and is a leading cause of disability in people aged 60 years and older.3 Several types of dementia exist; Alzheimer’s disease is the most common, followed by vascular dementia and rarer types of dementia, although mixed types of dementia often coexist.

Alcohol use has been associated with changes in cognitive health and dementia (appendix p 3). Briefly, the relationships between alcohol use and cognitive health in general and dementia in particular are complex.4 Most reviews point to a possible beneficial effect of light-to-moderate drinking on cognitive health. However, moderate drinking has been consistently associated with detrimental effects on brain structure,5 and nearly every review describes methodological problems of underlying studies, such as inconsistent measurement of alcohol use or dementia, or both, and insufficient control of potential confounders.

By contrast, heavy drinking seems detrimentally related to dementia risk, whatever the dementia type. First, ethanol and its metabolite acetaldehyde have a direct neurotoxic effect, leading to permanent structural and functional brain damage. Second, heavy drinking is associated with thiamine deficiency, leading to Wernicke–Korsakoff syndrome. Third, heavy drinking is a risk factor for other conditions that can also damage the brain, such as epilepsy, head injury, and hepatic encephalopathy in patients with cirrhotic liver disease. Fourth, heavy drinking is indirectly associated with vascular dementia because of the associations of heavy drinking with vascular risk factors such as high blood pressure, haemorrhagic stroke, atrial fibrillation, and
Research in context

Evidence before this study
Following the PRISMA guidelines, a systematic search was done using OVID to identify all work published from 2000 to Oct 3, 2017, on MEDLINE, Embase, and PsycINFO. Reviews on the effects of alcohol use on cognitive health were identified using a combination of keywords and Medical Subject Headings terms related to alcohol use, dementia, Alzheimer’s disease, brain function, memory, and cognitive health (appendix pp 3–7). 23 relevant systematic reviews were identified. For light-to-moderate drinking, most reviews reported some beneficial relationships, even though alcohol use seemed to be associated with structural brain damage at moderate levels of drinking. For heavy drinking, defined by WHO and the European Medicines Agency as drinking at least 60 g of pure alcohol per day for men and at least 40 g for women, most research pointed towards a detrimental effect of alcohol on cognitive health and an increased risk of dementia. Nearly every review describes methodological problems of underlying studies, such as under-representation of heavy drinkers in population-based cohorts; inconsistent measurement of alcohol use or dementia; or both; insufficient control of potential confounders; and insufficient consideration of sample attrition in patients with alcohol use disorders.

Added value of this study
Using a representative large cohort of all patients admitted to French hospitals between 2008 and 2013, we found a strong association between alcohol use disorders and dementia. Under the age of 65 years, most prevalent cases of dementia were either alcohol related by definition, or patients qualified for a diagnosis of alcohol use disorders. Alcohol use disorders contributed markedly to dementia incidence, and were associated with all types of dementia over the lifetime. Thus, heavy drinking should be considered as one of the major risk factors for this cluster of diseases. Screening, brief interventions for heavy drinking, and treatment for alcohol use disorders should be implemented to reduce the alcohol-attributable burden of dementia.

Methods

Study design
The data source for this study was the French National Hospital Discharge database (Programme de Médicalisation des Systèmes d’Information), which contains all public and private claims for acute inpatient and day-case hospital admissions, post-acute care, and psychiatric care since 2008. The standardised discharge summary includes patient demographics (sex, age at entry, and postal code of residency); primary and associated discharge diagnosis codes according to the WHO International Classification of Diseases, tenth revision (ICD-10); medical procedures received; length of stay; and discharge modes (including in-hospital death). Using unique anonymous identifiers, the hospital trajectory of each patient could be traced from 2008 to 2013.

We included all patients aged 20 years and older residing in metropolitan France who were discharged in the years 2008–13. Following ICD-10 taxonomy, we excluded all patients discharged with diseases that can lead to rare types of dementia (F02): infectious diseases including HIV/AIDS, hereditary metabolic disorders, hereditary neurological disorders including Huntington’s disease, other neurological disorders including Parkinson’s disease, and systemic connective tissue disorders. We also excluded patients with early-life mental disorders that could increase or confound dementia diagnosis, including cerebral palsy, Down’s syndrome and other learning disabilities, and schizophrenia. The full coding dictionary of exclusion criteria, dementia case definitions, and risk factors assessed before dementia onset is provided in the appendix (p 14–18).

The study was approved by the French National Commission for Data Protection (CNIL DE-2015-025), who granted access to the French National Hospital Discharge database for the years 2008 to 2013. The requirement for informed consent was waived because the study used de-identified data.

Procedures

The primary exposure was alcohol use disorders and the main outcome was dementia. Dementia was defined by any primary or associated discharge diagnosis (ICD-10) codes labelling dementia (F00-F03, F05.1, F1x.73, or G30) or related to dementia (other degenerative diseases of the nervous system [G31], progressive vascular leukoencephalopathy [I673], or senility [R54]).

Dementia onset was defined by the age at first dementia diagnosis recorded from 2008 to 2013; diagnoses made
before age 65 years were classed as early-onset dementia. Dementia onset was separated into three categories: alcohol-related brain damage (F10.73, G31.2); vascular dementia; and other dementia, including Alzheimer’s disease. Vascular dementia was broadly defined by any record of vascular dementia, mixed dementia, or progressive vascular leukoencephalopathy as well as any dementia with a history of stroke or transient ischaemic attack.26

Alcohol use disorders were identified by two categories of discharge diagnosis (ICD-10) codes: mental and behavioural disorders due to former or current chronic harmful use of alcohol (F10.1–F10.9, Z50.2), including alcohol abstinence (F10.20–F10.23); or chronic diseases attributable to alcohol use disorders (eg, K70 for alcoholic liver disease).26 Alcohol-related conditions were Wernicke-Korsakoff syndrome, end-stage liver disease and other forms of liver cirrhosis, epilepsy, and head injury.

Vascular risk factors were tobacco smoking, obesity (body-mass index ≥30 kg/m²), high blood pressure, hyperlipidaemia, and diabetes.1 Cerebrovascular diseases included haemorrhagic stroke, ischaemic stroke, a history of stroke, a history of transient ischaemic attack, and cerebrovascular diseases other than stroke, all assessed before stroke. Other cardiovascular diseases were ischaemic heart disease, peripheral arterial disease, atrial fibrillation, and heart failure.

Educational level is not recorded in the standardised discharge summary. We used 5645 postal codes of residency as a proxy of educational level and for each geographical area compared the proportion of adults at older landmark ages on Jan 1, 2011, other established risk factors for dementia included depression and hearing loss.1 Additionally, we controlled for possible risk factors for dementia, including visual impairment that might result from retinopathy or glaucoma,1 sleep apnoea,1 and other diseases that might lead to rare types of dementia (ie, chronic kidney disease including uraemia, hypothyroidism including myxoedema, and infectious diseases of the CNS including encephalitis).

**Statistical analysis**
All analyses were stratified by sex because men have shorter life expectancy and higher incidence of almost all risk factors considered. We initially studied prevalent dementia cases in 2008–13 and the distribution of alcohol-related brain damage and other alcohol use disorders by age at dementia onset. Because dementia is often associated with long diagnosis delays and associations of risk factors with dementia could be confounded by reverse causation,26 we conservatively studied risk factors for incident dementia among patients admitted to hospital from 2011 to 2013 who had no record of dementia from 2008 to 2010.26 The effects of alcohol use disorders and other risk factors on dementia onset, overall and by type, were estimated in multivariate Cox proportional hazards models without variable selection. Age was used as the timescale to estimate adjusted hazard ratios (HRs) and 95% CIs, with follow-up starting from Jan 1, 2011 (with independent left truncation on Jan 1, 2011) until dementia onset, in-hospital death, or right-censoring at last hospital discharge from 2011 to 2013.27,28,20 Observed non-proportional hazards were accounted for by including all risk factors as age-varying variables; alcohol use disorders, tobacco smoking, and personal histories of conditions (head injury, stroke, transient ischaemic attack, or myocardial infarction) were considered in the risk set starting from Jan 1, 2011, and other risk factors were conservatively identified at first hospital record.27 All Cox models were stratified by patient residency area across 21 French administrative regions (Corsica was included in the Provence-Alpes-Côte d’Azur region), having received care in a teaching hospital, and the first year of hospital admission from 2008 to 2013 to account for geographical and temporal variations in alcohol use exposure and dementia diagnosis as well as possible levels of misclassification for all variables.

We did several sensitivity analyses to ascertain the effects of alcohol use disorders on dementia onset. First, we used definitions of dementia restricted to primary discharge diagnosis codes of dementia; ICD-10 codes labelling dementia, overall or by dementia type (vascular dementia, Alzheimer’s disease); and severity level (first diagnosis of mild cognitive impairment without or before dementia, first diagnosis of dementia at a severe stage). Second, we considered the full sample, while all exclusion criteria were introduced among previous covariates. Third, we selected study populations at older landmark ages on Jan 1, 2011 (≥45 years, ≥55 years, ≥65 years, ≥75 years, or ≥85 years). Finally, the effects of alcohol abstinence (in people with previous alcohol use disorders) and other uncontrolled alcohol use disorders on the risks for dementia onset and in-hospital death were contrasted over the lifetime by use of a third-order polynomial of age on Jan 1, 2011, in Cox models adjusted for proxy of educational level and vascular risk factors, and stratified by previous variables.

We did a falsification analysis in all Cox multivariate models, which relies on disease controls selected for their unknown and therefore unlikely association with an outcome.27 If no association is found for the disease controls in a large dataset such as a national hospital discharge database, it supports the validity of the associations found for the risk factors under study. We used cancer as a control, separated into three disease categories in relation to prognosis and possible association with dementia onset: cancer or metastasis of the CNS, other non-melanoma skin cancer assessed before brain metastasis, and non-melanoma skin cancer. All analyses were done in SAS (version 9.4).
Role of the funding source
There was no funding source for this study. The corresponding author had full access to all the data in the study and all authors had final responsibility for the decision to submit for publication.

Results
Of 31624156 adults discharged from French hospitals from 2008 to 2013, 1328191 (4.2%) were diagnosed with dementia (appendix p 20). We excluded 1066019 patients (3.4%) with diseases that can lead to rare types of dementia or with early-life mental disorders that can increase or confound dementia diagnosis (218848 [20.5%] dementia cases; appendix p 20).

720215 (64.9%) of the 1109343 dementia cases were women (figure 1). The proportion of women increased with age at dementia onset. Conversely, 37233 (64.9%) of the 57353 (5.2% of total) early-onset dementia cases were men.

945512 (3.1%) of 30558137 adults were discharged with alcohol use disorders (712583 [5.5%] of 12941788 men and 232929 [1.3%] of 17616349 women), of whom 816160 (86.3%) qualified for alcohol dependency and 140312 (14.8%) had at least one period of alcohol abstinence in 2008–13. Alcohol-related brain damage was recorded in 35034 dementia cases and other alcohol use disorders in 52625 (figure 1). Both conditions were more frequently recorded in men (26084 [74.5%] and 35006 [66.5%], respectively; p<0.0001) and accounted for 32453 (56.6%) of 57353 early-onset dementia cases (22338 [38.9%] and 10115 [17.6%], respectively).

Of 8295081 men discharged from 2011 to 2013, 181255 (2.2%) were newly diagnosed with dementia at a median age of 82 years (IQR 75–87; table). Alcohol use disorders were recorded in 512473 (6.2%) men and 29944 (16.5%) of men with dementia. Alcohol use disorders were associated with an increased risk for dementia onset among men (HR 3.36, 95% CI 3.31–3.41). Alcohol use disorders were the strongest modifiable risk factor for dementia onset in men (figure 2).

Regarding dementia type, 12435 (6.9%) of 181255 men with newly diagnosed dementia had alcohol-related brain damage at a median age of 60 years (IQR 53–69; appendix p 23). The strongest association with alcohol-related brain damage was with end-stage liver disease (3593 [28.9%], HR 27·28, 95% CI 26·00–28·61) followed by liver cirrhosis (2491 [20.0%], 23·50, 22·29–24·78). Several risk factors independently contributed to alcohol-related brain damage, in particular all alcohol-related conditions and tobacco smoking (HR >2 for all; appendix p 23).

Compared with alcohol-related brain damage, dementia onset was significantly delayed in other dementia types (p<0.0001). Of 181255 men with newly diagnosed dementia, 69700 (38.5%; median age 82 years, IQR 77–87) had vascular dementia (appendix p 24) and 99120 (54.7%; 83 years, 77–87) had other dementia (appendix p 25). Alcohol use disorders were more frequently recorded in vascular dementia (11.2%) than in other dementia (9.8%; p<0.0001). In multivariate Cox analyses, alcohol use disorders remained associated with an increased risk for each dementia type (vascular dementia HR 2.30, 95% CI 2.24–2.36; other dementia 2.36, 2.31–2.42).

Of 11474359 women discharged from 2011 to 2013, 322261 (2.8%) were newly diagnosed with dementia (table). Incidence of dementia was lower in women than
### Table: Risk factors for dementia onset

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>1·19 (1·15–1·20)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1·45 (1·40–1·50)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>History of stroke</td>
<td>1·11 (1·05–1·17)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>history of transient ischaemic attack</td>
<td>1·07 (1·03–1·11)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Cerebrovascular disease other than stroke</td>
<td>1·02 (1·00–1·05)</td>
<td>0·0096</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>1·04 (1·02–1·06)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>1·02 (1·00–1·04)</td>
<td>0·0108</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1·07 (1·05–1·08)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1·02 (1·00–1·04)</td>
<td>0·0061</td>
</tr>
<tr>
<td><strong>Other risk factors for dementia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residency area with less education, third quartile</td>
<td>1·05 (1·02–1·08)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Residency area with less education, fourth quartile</td>
<td>1·07 (1·05–1·09)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Depression</td>
<td>1·02 (1·00–1·04)</td>
<td>0·0075</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>1·00 (0·98–1·02)</td>
<td>0·762</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>1·00 (0·98–1·03)</td>
<td>0·996</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>1·05 (1·03–1·07)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>1·01 (0·99–1·02)</td>
<td>0·0093</td>
</tr>
<tr>
<td>Chronic kidney failure</td>
<td>1·00 (0·98–1·02)</td>
<td>0·644</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1·01 (0·99–1·03)</td>
<td>0·375</td>
</tr>
<tr>
<td>Infectious diseases of the CNS</td>
<td>1·00 (0·99–1·02)</td>
<td>0·833</td>
</tr>
<tr>
<td><strong>Non-cardiovascular diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer or metastasis of the CNS</td>
<td>1·02 (1·01–1·04)</td>
<td>&lt;0·0001</td>
</tr>
<tr>
<td>Any cancer other than non-melanoma skin cancer</td>
<td>1·01 (0·99–1·03)</td>
<td>0·0093</td>
</tr>
<tr>
<td>Non-melanoma skin cancer</td>
<td>1·00 (0·98–1·02)</td>
<td>0·996</td>
</tr>
</tbody>
</table>

Data are median (IQR) or number (%). Table shows adjusted HRs from multivariate Cox regressions for incident dementia (newly diagnosed at hospital in 2011–13 with no recorded dementia in 2008–10). Details of selection of the study population are provided in the appendix (p 20). HR=hazard ratio.
men up to age 80 years (appendix p 19). Collectively, the median age at dementia onset was significantly delayed in women compared with men (85 years, IQR 80–89 vs 82 years, 75–87; \( p < 0.0001 \)), with significantly fewer reports of alcohol-related brain damage (4281 [1.3%] and 12435 [6.8%], respectively) and vascular dementia (104113 [32.3%] and 69700 [38.5%], respectively; \( p < 0.0001 \)).

Alcohol use disorders in women were similarly associated as in men, with an increased risk for dementia onset (HR 3.34, 95% CI 3.28–3.41) and were the strongest modifiable risk factor for dementia onset in women (figure 2). About the same independent risk factors for dementia onset were identified for both sexes (adjusted HRs >1): all alcohol-related conditions; tobacco smoking, high blood pressure, and diabetes among vascular risk factors; haemorrhagic stroke, ischaemic stroke, a history of stroke, peripheral arterial diseases (in men), atrial fibrillation, and heart failure among cardiovascular diseases; and patient residency area with less education, depression, hearing loss, chronic kidney failure, hypothyroidism, and infectious disease of the CNS among other risk factors (table).

However, except for depression and hypothyroidism, alcohol use disorders and all other independent risk factors for dementia were significantly less frequently recorded in women than in men (appendix p 21). In addition, except for alcohol use disorders, atrial fibrillation, lower education attainment, and hypothyroidism, strengths of association of the risk factors with dementia onset were significantly different between the sexes: higher in men for alcohol-related conditions, stroke, heart failure, depression, hearing loss, and infectious diseases of the CNS; and higher in women for vascular risk factors and chronic kidney failure (table; \( p < 0.05 \) for all).

The main study results were generally supported by sensitivity and falsification analyses. Alcohol use disorders were strongly associated with dementia onset for any case definition of dementia (figure 3; appendix pp 27–32), and when the full sample was considered with all exclusion criteria introduced among previous covariates (appendix pp 33–34). In other sensitivity analyses in older study populations selected on Jan 1, 2011, alcohol use disorders remained strongly associated with late-onset dementia (appendix pp 35–39). Compared with uncontrolled alcohol use disorders (appendix p 40), alcohol abstinence was significantly associated with lower risks of competing mortality over the lifespan, although no risk reduction was observed for dementia onset (appendix pp 41–44). Finally, regarding the falsification analysis, none of the cancer categories was associated with dementia onset, irrespective of cancer site (table) and prognosis (appendix p 26).

**Discussion**

In this nationwide study, we found a marked association of alcohol use disorders with all types of dementia, even after controlling for potential confounding risk factors. The overall HR for onset of all types of dementia was above 3.3, and for vascular and other dementia remained above 2.3 for both sexes. The association with alcohol use disorders was especially important in those with early-onset dementia, with most patients having alcohol-related brain damage or an additional diagnosis of alcohol use disorders. This finding corroborates other results, which suggested alcohol is a risk factor for early-onset dementia in men.10

The French health-care system provides not only universal, but also liberal access to hospital care with minimal out-of-pocket expenses. Consequently, more than 80% of French adults older than 65 years (50% before that age) were admitted to hospital over the 6-year study period (appendix p 45), supporting a high generalisability.

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**Figure 2: Potentially modifiable risk factors for dementia among men (A) and women (B)**

Bars are 95% CIs.
of the study findings to the French population as well as populations with similar exposure to the risk factors in general, and to alcohol use disorders in particular.

However, several potential limitations of our study should be acknowledged, including misclassified and missing variables due to the administrative recording of data. One limitation relates to the assessment of dementia, overall and by type. Although the French claims database is subject to high levels of quality control, all ICD-10 codes of dementia recorded as secondary discharge diagnoses (except senility) would be associated with better hospital reimbursement. Indeed, only 188 841 (37·5%) of 503 516 new dementia cases were identified as the primary discharge diagnosis for both sexes (appendix p 27). However, an opportunistic, up-coding bias seems equivocal because the comparison of incidence by sex and age with the reference cohort study done in the southwest of France showed no clear differences (appendix p 19) and differences are likely to be attributed to unstable estimates caused by the small sample size in the reference cohort study (190 new dementia cases over 5 years).

Diagnosis of dementia type remains probabilistic without brain autopsy, as is the case in most epidemiological studies. Accordingly, we included 122 903 new patients identified with ICD-10 codes related to dementia, because 37 951 (30·9%) were eventually diagnosed with ICD-10 codes labelling dementia in the follow-up. Because of our study aim, we unconventionally prioritised alcohol-related brain damage and vascular dementia over Alzheimer’s disease. Accordingly, the proportion of vascular dementia cases recorded of the 503 516 new dementia cases almost doubled from 96 252 (19·1%) with use of ICD-10 codes for vascular dementia, a rate usually reported, to 173 181 (34·5%) with additional use of any record of mixed dementia or dementia with a history of stroke or transient ischaemic attack. However, the main study findings were corroborated in all sensitivity analyses done on dementia case definition.

A second limitation relates to the identification of alcohol use disorders and other risk factors for dementia. Even though alcohol use disorders were identified by several sources of medical information including post-acute rehabilitation over 6 years, alcohol use disorders were most likely underestimated compared with prevalence estimates for France (16·7% for men and 5·4% for women). Alcohol use disorders are highly stigmatised, with low treatment rates of around 10% in Europe; thus, probably only the more severe cases with alcohol dependence were recorded at hospital. However, such a bias would translate into a potential underestimation of the effect of alcohol use disorders on dementia onset.

Similarly, vascular risk factors were probably underestimated. However, except high blood pressure, the effects of vascular risk factors on dementia onset are probably mediated by cerebrovascular diseases that are measured exhaustively at hospital and were adjusted for in all multivariate analyses. In this regard, we found that obesity and hyperlipidaemia were not independently associated with dementia onset, in agreement with recent reviews.

A final limitation concerns the fact that assessments using large-scale administrative databases are typically overpowered to find statistical differences, which is true for the French National Hospital Discharge database. However, we did a falsification analysis by adding cancer controls to all analyses. None of the cancer controls were associated with dementia onset, supporting the main study findings. Additionally, the effect sizes of alcohol
use disorders on dementia onset were substantial and would have probably been significant in epidemiological studies with smaller sample sizes if patients with alcohol use disorders were included and alcohol exposure was assessed. Overall, although misclassification and missing variables might have biased our findings, these biases would have been mainly in the direction of underestimation.

Findings from this nationwide study suggest that the burden of dementia attributable to alcohol is much larger than previously thought. In multivariate analyses, alcohol use disorders were the strongest modifiable risk factor for dementia onset. Additionally, although alcohol abstinence was expectedly associated with a lower risk of competing death compared with uncontrolled alcohol use disorders, the study findings show that the risk for dementia onset remained unchanged after abstinence. This finding corroborates recent results showing that alcohol use directly exerts lifelong brain damage.16 Finally, alcohol use disorders were associated with all other independent risk factors for dementia onset, suggesting that alcohol use disorders contribute in many ways to the risk of dementia.

In summary, our study findings support that alcohol use disorders should be recognised as a major risk factor for all types of dementia. Alcohol-related dementia should be recognised as one of the main causes of early-onset dementia.2,4 Additionally, clinicians should be better aware of the role of alcohol use disorders in dementia onset over the lifetime, which seems to be a risk factor often omitted.1 Early detection, brief interventions (ie, short, structured motivational interviews to support individuals to change alcohol-related behaviour), and treatment for alcohol dependence or less severe alcohol use disorders are effective and even cost-effective measures in primary care.10 Alcohol policy measures, such as reduction of availability, increase of taxation, and ban on advertising and marketing, have also proven to be effective and cost-effective, although these measures have tended not to be popular with governments. For instance, the ban on alcohol advertisements was recently repealed in France.11 If all these measures are implemented widely, they could not only reduce dementia incidence or delay dementia onset, but also reduce all alcohol-attributable morbidity and mortality.12

Contributors
MS conceptualized the study, contributed to the analysis and interpretation of the data, and co-wrote the first draft of the paper. BGF and CD contributed to the clinical and epidemiological implications sections, and helped shape the overall interpretation. OSMH and JR did the systematic search and screened the results for inclusion. JR also contributed to the analysis and interpretation of the data and co-wrote the first draft of the paper.

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Declaration of interests
MS is the founder and CEO of THEN (Paris, France), which received research grants from AbBiVe, Gilead, Merck, and Novartis. All other authors declare no competing interests.

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Alcohol and dementia: a complex relationship with potential for dementia prevention

The relationship between alcohol and dementia prevention has been widely studied, but most studies have focused on the potential for modest alcohol consumption to reduce the risk of dementia. These, primarily cohort, studies have varied in terms of the types of alcohol and thresholds of consumption assessed and have typically used self-reported consumption. Nonetheless, a J-shaped relationship has been fairly consistently reported between alcohol consumption and dementia risk, with moderate consumption associated with better outcomes than heavy consumption or non-consumption, although for non-drinkers there might be other confounders.\(^1,2\)

Published studies are interesting and pose questions such as whether modest consumption of red wine could be protective as part of a Mediterranean diet.\(^3\) However, the potential for substantial alcohol consumption, equivalent to 7–8 units a day for men and 5 units a day for women in most studies, to be a substantial risk factor for dementia is often overlooked.\(^4,5\) The effect of alcohol use disorders specifically on dementia has received very little attention, although an association with an increased risk of cognitive decline has been suggested.\(^6\)

In The Lancet Public Health, Michaël Schwarzinger and colleagues\(^7\) present their findings from a large retrospective study of data from over 31 million people aged at least 20 years from the French National Hospital Discharge database, including over 1 million people with an International Classification of Diseases, tenth revision (ICD-10) diagnosis of some form of dementia. Alcohol-related brain damage or alcohol use disorders based on ICD-10 codes were recorded in more than 85 000 of those who developed dementia, with a hazard ratio greater than 3 for the association between alcohol use disorders and dementia for both sexes (3.34, 95\% CI 3.28–3.41 for women and 3.31–3.41 for men). The importance of alcohol use disorders was particularly striking in people with early-onset dementia: 57\% of people with a diagnosis of early-onset dementia also had an alcohol use disorder. Schwarzinger and colleagues modelled the importance of alcohol use disorders and suggested their effect might be greater than that of recognised risk factors such as smoking, depression, and hypertension. Their study is immensely important and highlights the potential of alcohol use disorders, and possibly alcohol consumption, as modifiable risk factors for dementia prevention.

Schwarzinger and colleagues discuss potential mechanisms, including a direct neurotoxic effect of ethanol and metabolites; thiamine deficiency; consequences of heavy alcohol use such as hepatic encephalopathy, epilepsy, and head injury; and increased occurrence of comorbid medical and lifestyle risk factors for dementia.\(^4,8\) An important caveat is that people with Down’s syndrome and other learning disabilities—a group at major risk of early-onset dementias—were excluded from the study.

Many reports addressing dementia risk, such as the Lancet Commission on dementia prevention, intervention, and care,\(^8\) have not highlighted alcohol use disorders as a substantial attributable risk factor for dementia. The focus on the potential protective effects of modest alcohol use has probably complicated the analysis and interpretation of previous findings, and the potential importance and effect of heavy alcohol use as a modifiable risk factor for dementia has probably been overlooked.

Several issues still need to be addressed. One is the relationship between alcohol use disorders and related comorbidities. Alcohol use disorders are probably associated with poor diet and lifestyle, smoking, cardiovascular comorbidity, lower adherence to medical treatments, depression, and potentially social isolation. Schwarzinger and colleagues’ used a crude, area-based measure of socioeconomic status, and exploration of this aspect of the relationship between alcohol use disorders and dementia in more detail will be important. Understanding the significance of these risk factors, and the pathways of risk impact in people with alcohol use disorders, will help us to model the attributable risk more accurately and to develop better prevention strategies for people with alcohol use disorders.

Additional questions relate to the threshold of alcohol consumption and potential cross-cultural differences. In the study by Schwarzinger and colleagues, the focus was on a diagnosis of alcohol use disorders rather than...
a threshold of alcohol consumption: individuals with alcohol use disorders had this information captured in a hospital database, having been identified as having problems related to their alcohol use. Alcohol use disorders and alcohol consumption volumes are related but distinct, and work is needed to clarify whether there is an association of similar magnitude between alcohol consumption volumes and dementia or whether associated problems and medical and psychiatric comorbidity drive the risk. A related question is whether the importance of alcohol consumption and alcohol use disorders as a risk factor varies depending on national mean alcohol consumption; for example, France consumes 12.2 L per person per year, much higher than Italy (6.7 L per person per year) and India (4.3 L per person per year).9

Although many questions remain, several can be answered using existing data, which would provide an opportunity to refine our understanding of the pathways of modifiable risk and develop optimal prevention strategies. In our view, this evidence is robust and we should move forward with clear public health messages about the relationship between both alcohol use disorders and alcohol consumption, respectively, and dementia. Following the Rose population principle,10 we might want to consider the extent to which the growing prevalence of dementia worldwide might be curbed by reductions in population-level alcohol consumption.

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